Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition while Promoting Human Health

Part I: Rationale and Avenues toward a *Green Pharmacy*

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Environmental Health Perspectives pre-publication online citation:

Daughton CG. 2003. "Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition while Promoting Human Health -- Part I: Rationale and Avenues toward a Green Pharmacy," Environ. Health Perspect. doi:10.1289/ehp.5947. [online 12 December 2002: http://ehpnet1.niehs.nih.gov/docs/2003/5947/abstract.html]

running title:
Pollution Prevention for Drugs in the Environment — Part I

key words:
drugs, pollution prevention, environmental pollution, cradle-to-cradle stewardship, green pharmacy

acronyms:
ADR: adverse drug reaction
CCL: Contaminant Candidate List
EEC: expected environmental concentration
EMEA: The European Agency for the Evaluation of Medicinal Products
FDA: U.S. Food and Drug Administration
IOM: Institute of Medicine
MOA: mechanism of action
NSAID: non-steroidal anti-inflammatory
PEC: predicted environmental concentration
PPCPs: pharmaceuticals and personal care products
OTC: over the counter
TM/CAM: traditional, complementary, and alternative medicine
USP: United States Pharmacopeial Convention, Inc.
WHO: World Health Organization

NOTICE: The U.S. Environmental Protection Agency (EPA), through its Office of Research and Development (ORD), funded and performed the research described. This manuscript has been subjected to the EPA's peer and administrative review and has been approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation by EPA for use. The author thanks the following people for their valuable time in providing helpful review of both technical and policy aspects of this manuscript: Octavia Conerly (U.S. EPA, Office of Water) and EHP's anonymous reviewers, all of whom contributed to improving the quality of the manuscript.

ABSTRACT

Since the 1980s, the occurrence of pharmaceuticals and personal care products (PPCPs) as trace environmental pollutants, originating primarily from consumer use and actions as opposed to manufacturer effluents, continues to become more firmly established. Although PPCPs have typically been identified in surface and ground waters, some are also undoubtedly associated with solid phases such as suspended particulates, sediments, and sewage sludges, despite their relatively high affinity for water. Often amenable to degradation, their continual introduction to waste-receiving waters results from their widespread, continuous, combined usage by individuals and domestic animals, imparting them with a "pseudo-persistence" in the environment. Little is known regarding the environmental or human health hazards that might be posed by chronic, sub-therapeutic levels of these bioactive substances or their transformation products. The continually growing, worldwide importance of freshwater resources, however, underscores the need for ensuring that any aggregate or cumulative impacts on (or from) water supplies be minimized.

Despite the paucity of effects data from long-term, simultaneous exposure at low doses to multiple xenobiotics (particularly non-target-organism exposure to PPCPs), a wide range of proactive actions could be implemented for reducing or minimizing the introduction of PPCPs to the environment. Most of these actions fall under what could be envisioned as a holistic stewardship program — overseen by the healthcare industry and consumers alike. Significantly, such a stewardship program would benefit not just the environment — additional, collateral benefits could automatically accrue, including the lessening of medication expense for the consumer and improving patient health and consumer safety.

This paper (the first of two parts describing the "green pharmacy") initially focuses on the background behind the imperative for an ecologically oriented stewardship program for PPCPs. It then presents a broad spectrum of possible source control/reduction actions, residing more under the control of the

health-care industry, that could minimize the disposition of PPCPs to the environment. The second part deals with those activities tied more closely to the end user (e.g., the patient) and the issues associated with drug disposal/recycling.

This two-part document attempts to cohesively capture for the first time the wide spectrum of actions available for minimizing the release of PPCPs to the environment. A major objective is to generate an active dialog or debate across the many disciplines that must become actively involved to design and implement a successful approach to life-cycle stewardship of PPCPs.

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INTRODUCTION

The occurrence of pharmaceuticals and personal care products (PPCPs) in the environment has received growing attention since the 1980s. The major issues associated with the origins and occurrence of these chemicals in surface, sub-surface, and drinking waters (as well as what little is known about the potential for effects on non-target species) have been captured in a number of reviews, books and proceedings, examples of some recent ones of which include Daughton (2001a), Daughton and Jones-Lepp (2001), Daughton and Ternes (1999), Heberer (2002; as well as the entire special issue of *Toxicology Letters* [2002]), Kümmerer (2001), and Servos et al. (2002). The most comprehensive target-monitoring study ever performed was completed by the USGS (Kolpin et al. 2002). Many of these materials (and more) are accessible from the U.S. Environmental Protection Agency (EPA) web site devoted to the topic of PPCPs in the environment (Daughton/EPA 2002a).

This paper is the first of a two-part examination (Daughton 2003a,b) of the many facets of a little-discussed, but very important, aspect of the overall issue of PPCPs as environmental pollutants — namely, pollution prevention. In light of the fact that trace residues from this large, diverse galaxy of sometimes highly bioactive chemicals gain entry to the environment simply by way of their usage and

disposal, and regardless of what little is known regarding the consequences for ecological or human health (Daughton 2001a, Daughton and Ternes 1999), a wide spectrum of actions could be taken to minimize or eliminate their continued environmental disposition. Significantly, these actions toward pollution prevention (e.g., source reduction/control) hold the potential at the same time for beneficial human health consequences unrelated to their occurrence as pollutants. This first of two parts (Daughton 2003a) focuses on those aspects of source control/reduction that reside more under the control of the health-care industry (further up the chain of events involved with a drug's cradle-to-grave disposition), while the second part (Daughton 2003b) deals with those activities tied more closely to the end user (e.g., the patient) and issues associated with drug disposal/recycling. The first part also presents some of the background and context for why pollution prevention is a topic worth considering for PPCPs, whereas the second part makes specific suggestions and recommendations centering more on end-use, presents recommendations for further research, and poses some considerations with regard to the future.

With its focus on pollution prevention (e.g., source elimination or minimization) via voluntary actions, as an alternative to conventional pollution control via prescribed standards, this two-part paper is intended as a companion piece to the review (Daughton and Ternes 1999) published in *Environmental Health Perspectives* that focused primarily on the origins and environmental occurrence of PPCPs together with an introduction to what little was known at that time about the potential for adverse ecological effects.

One of the major objectives of this paper is to generate an active dialog or debate across the many disciplines that must become actively involved to design and implement a successful approach to life-cycle stewardship of PPCPs — an approach that not only minimizes their potential to impact the environment, but one that also could collaterally improve medical healthcare outcomes for consumers and reduce healthcare costs. While the onus for environmental stewardship primarily rests with the larger healthcare community (including the consumer), almost no discussion of the overall issue has taken root in the medical literature (Daughton 2002a). A cohesive, scientifically sound set of guiding principles could be adopted by the industries involved with manufacturing, packaging, distribution, and purveyance of PPCPs — principles that would also serve to influence or guide consumer actions. By focusing on developing an industry consensus and cultural mind set toward holistic environmental responsibility, rather than relying on compliance to regulations, all sectors of society could play integral, productive roles in striving for a sustainable environmental environment.

Opportunity for Caution — Toxicity Out of Context: While PPCPs are often referred to as "emerging" pollutants, it is reasonable to surmise that the occurrence of PPCPs in waters is not a new phenomenon. Their occurrence has only become more widely evident since the 1990s because continually improving chemical analysis methodologies have lowered the limits of detection for a wide array of xenobiotics in environmental matrices. There is no reason to believe that any given PPCP has not had the potential to find its way into the environment since the date of its introduction to commerce — or even from the date it was first used on an experimental or clinical trial basis.

Most current approaches to pollutant tracking center on the small subset of anthropogenic (and some naturally occurring) toxicants in the environment. Significantly, these "conventional" pollutants do not necessarily serve as surrogates representing the extremely wide spectrum of modalities by which toxicants can adversely affect organisms. That regulated pollutants account for such a small fraction of

potential chemical stressors begs a question that can be formulated from a notion often attributed to Einstein, paraphrased as "Not everything that can be counted counts, and not everything that counts can be counted." A corollary can be derived from this for environmental monitoring: "Not everything that can be measured is worth measuring, and not everything worth measuring is measurable." The spectrum of pollutants typically identified in an environmental sample represent but an unknown portion of those actually present (possibly very small), and they are of unknown overall risk significance (Figure 1).

Because of the extraordinary complexity of the nature of exposure and outcome, toxicologists are usually forced to look at cause-effect issues "out of context" — the historic ramification has been to consider exposure solely as a function of a single toxicant or a very limited set of chemical stressors. The overall picture, however, is complicated not just by the large universe of potential toxicants to which an organism can normally be exposed at any point (or period) of time, but also by the host of other variables such as exposure level, exposure route (e.g., dermal, enteral, pulmonary), exposure timing (windows of vulnerability such as developmental stage), prior exposure history, prior exposure duration such as acute (short-term, sequential, intermittent, episodic) or chronic, nutrition, age, sex, genetics, and non-chemical co-stressors (temperature, physical/metabolic stress, noise, electromagnetic radiation, pathogens). All of these factors determine an organism's historic "exposure trajectory," which in turn determines its current health status and sets the stage for the outcome of current exposure (vulnerability versus resistance to homeostasis perturbation). With science's limited understanding of this complex, dynamic interplay of a multitude of factors, risk assessment is necessarily restricted to assessing the ramifications of potential adverse toxic events out of context of the larger puzzle — without the larger holistic perspective.

A convenient short-hand term that captures the complete context of an organism's cumulative exposure to chemical stressors does not exist. One possibility offered here is Toxicant Totality Tolerance Trajectory (abbreviated "4T's"), which accounts for an organism's complete exposure time line (a

trajectory described by prior multi-dimensional exposure history) and the fact that a major objective of all organisms is to maintain homeostasis (in the face of continual perturbation by stressors). Homeostasis can be maintained only within the tolerance bounds for the organism's biochemical defensive repertoire. So the 4T's describe the hypothetical overall true risk as reflected by the sum total of exposure to all toxicants (anthropogenic and naturally occurring) throughout the historical multi-dimensional space and trajectory of all other exposure variables. A key aspect to this concept is the critical state determined by the 4T's — the state at which an additional single exposure event can result in an adverse effect.

The documented occurrence of PPCPs in the environment may or may not eventually prove to have any implications with regard to either ecological or human health — primarily because their known concentrations are so low (ng/L [ppt] - µg/L [ppb]). The issues associated with potential ecological effects in particular cannot be resolved until aquatic and computational toxicologists (for an overview of computational toxicology, see Bradley 2002) begin evaluating the effects on non-target organisms by simultaneous, long-term exposure to multiple PPCPs at low doses and to assess the significance of cumulative exposure to PPCPs sharing the same biochemical mechanism of action (MOA). Indeed, therapeutic doses for target organisms (which are often many orders of magnitude higher than dissolved waste concentrations) may not be relevant benchmarks against which to assess risks to non-target species. Furthermore, environmental monitoring tends to focus on concentrations of PPCPs dissolved in water (because of their water solubility). This emphasis, however, could possibly underestimate environmental loads by unknown magnitude because of sorption to suspended particulates, sediments, or sewage biosolids; this could prove critically significant with regard to interface phenomena and lead to higher than projected exposure levels (e.g., exposure to microorganisms to antibiotics).

Given the ever-expanding universe of receptors targeted for drug action, the futility of attempting to assess environmental effects using a chemical-by-chemical approach (indeed, the traditional approach has

relied only on lists of pre-selected, individual chemicals) becomes clearer as advances in drug design continue. Instead, the focus needs to be directed to understanding the ramifications of entire classes that share a common MOA (or common physiological or behavioral endpoint) — because of the probability of cumulative exposure. Delineating the total environmental burden of chemicals sharing a particular MOA could be the objective instead of targeting specific chemicals for regulation. First, however, those MOAs or cellular processes that pose inherent risks would have to be identified and prioritized, including significant effects or perturbations to homeostasis that are (1) unique to each therapeutic class (e.g., resistance-selection for antibiotics), and (2) mediated via biochemical features and pathways that are evolutionarily conserved across taxa and which are elicited by many therapeutic classes (e.g., efflux pumps, cellular stress protein response, apoptosis, specific signaling pathways, etc.). Many of these same toxicological issues are discussed in a recent overview (WHO 2002a) of "endocrine disrupting compounds" (EDCs), a small sub-set of which are PPCPs; an EDC is an exogenous substance that "alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." Although the topics of PPCPs and EDCs only partly intersect, they share some controversial commonalities.

A critical aspect of determining the significance of MOAs must be factored into this process. MOAs that lead directly to adverse effects are not the only consideration — or, paradoxically, not even necessarily the most important. Chemicals having no inherent toxicity of their own, but which rather potentiate the toxicity of others, might contribute significantly to risk. Examples include inhibitors of efflux pumps and of microsomal oxidases (Daughton and Ternes 1999; Daughton 2001a; Epel and Smital 2001). Finally arguing against the utility of MOA-directed risk assessments are two factors: (1) many drugs have multiple MOAs (these are sometimes referred to as "dirty" drugs), large numbers of which yet remain to be identified, and (2) gross, within-class endpoint differences are known to exist for certain drugs; as an example of the latter, some selective serotonin reuptake inhibitors (a class of antidepressants)

are extremely potent with regard to shellfish reproductive behavior while others have almost no effect (Daughton and Ternes 1999; Fong 2001).

Regardless of the risks that might be posed by the current generations of PPCPs, the very fact that many members of this large, diverse universe of bioactive chemicals have the demonstrated potential to enter the environment provides the rare opportunity to proactively investigate whether each of the myriads of new drugs under development poses adverse risks to the environment (or humans). This knowledge essentially affords us the luxury of an early-warning so as to direct more attention to potential, unintended ramifications of introducing new PPCPs to commerce. It gives us the advance opportunity to be watchful regarding the future introduction to commerce of drugs designed with completely new mechanisms of action and ever-increasing biochemical potencies.

But with this aside, there are many actions that can be taken in the shorter-term to minimize the introduction of PPCPs to the environment. These recommendations and suggestions are the subject of this paper. It is important to note that the ideas presented here are largely based upon the manner in which medical care (which includes pharmaceutical usage) is conducted in the U.S. and to lesser degrees in Canada, Western Europe, and Australia. The wide range of issues and suggestions presented here might have no relevance to other parts of the world (e.g., see below: "Connecting Health of Ecology and Human Health: Health Promotion & Social Entrepreneurs"). Also note that the major focus of this paper is a survey of the many avenues available for reducing the controllable introduction of PPCPs to the environment — the focus is not on the many issues (especially the potential for adverse effects) associated with the unintended, uncontrollable excretion of PPCPs and their metabolites into the environment (an issue that can be addressed via engineering "end-of-pipe" controls).

Fragmentation of Science: The many disciplines of science and other professions that need to be integrated in order to address the many facets of PPCPs as pollutants drives home the importance of cross-communication among disparate disciplines. Unfortunately, the fragmentation of science (driven by specialization) is a problem that continues to grow (Daughton 2001b, 2002b). This paper (parts I and II) attempts to weave together a good number of the many facets involved with pollution prevention aimed at PPCPs as environmental pollutants. In doing so, attempts are made to address two objectives. First is an effort to bring together the limited and fragmented literature that exists from the diverse fields and interwoven aspects involved with approaches for reducing the introduction of pharmaceuticals to the environment — in the face of what little is known regarding possible risks that might be associated with these bioactive substances in the environment. Second is an attempt to delineate some of the major actions that could be taken to minimize the introduction of drugs to the environment — actions that could be implemented with little planning, those that would require major attention by the numerous agencies involved with a patchwork of laws and regulation of drug recycling and disposal, as well as those that would require further research and development (R&D). A major motive for this paper is to foster an awareness of the many complexities involving this emerging issue — to open a door onto a wider perspective for and appreciation of the larger literature. While recognizing the importance of in-depth, critical reviews (Daughton 2001b, 2002b), the intent of this paper is not a comprehensive review of any of the many pertinent subjects or aspects, but rather to cite some key references so that those interested in pursuing particular aspects can gain faster entry to a literature that is often difficult to locate. Most of the literature covered in this article has never been synthesized into a unified "message" or understanding. The literature on pharmaceuticals encompasses a number of fields that are infrequently visited by environmental scientists. Likewise, those involved in medical science and health care practice are not fully informed of the environmental issues and consequences associated with drugs. It is hoped that these two disparate fields are brought together here, as much could be gained by their cross-collaboration.

Engaging the Public: The topic of PPCPs as pollutants has captured much attention by the press (Daughton/EPA 2002b), and its visibility with the public is marked by its introduction to educational curricula (from elementary school through college) and to the popular press (as an example, see Buhner 2002). The public, educators, and students have expressed much interest in the topic because they can identify easily with its primary origin, which embodies the interconnectedness of humans and the environment — the occurrence of PPCPs in the environment mirrors the intimate, inseparable, and immediate connection between the diffuse actions and activities of individuals and their environment (Daughton 2001a, Daughton/EPA 2002a). PPCPs owe their origins in the environment to their worldwide, universal, frequent, and highly dispersed but cumulative usage by multitudes of individuals. While the public has long understood that their individual actions and activities are partly responsible for terrestrial and air pollution (obvious examples being litter and vehicle exhaust), their connection with water pollution usually remains lost in the perception that industry and agriculture are the primary sources — not consumerism and personal activities. This is illustrated by the underappreciated fact that of the petroleum introduced to North American oceans each year, about 85% comes from the seemingly minuscule actions of individuals — not large oil spills and pipeline leaks (NRC 2002a). The strong interest expressed by the public in the topic of PPCPs grants scientists, educators, and policy makers a rare opportunity to engage consumers in learning about the environment and the many actions they can take as individuals to improve overall ecological and human health. Indeed, the critical importance of involving the public in scientific debates and decision making for creating sustainable communities is becoming more widely recognized (NCSE 2001).

Advance Warning: With regard to assessing environmental risk associated with PPCPs as pollutants, the focus of the science to date has been limited to the issues of environmental sources and occurrence — primarily chemical identities and concentrations in waters, and to a much lesser degree sewage sludge. Newer occurrence data is published on an ongoing basis from researchers in Europe, Canada, and the U.S.

One of the objectives of the first-ever U.S. national reconnaissance of "emerging pollutants" in waters, conducted by the USGS was to establish baseline occurrence data (Kolpin et al 2002; also: USGS 2002). Some further perspective on the USGS study is important, however. The PPCPs documented to occur in U.S. surface waters probably represent but a fraction of all those that actually occur (because the USGS monitoring study, like all monitoring studies, used a target-based approach, where only a limited number of compounds must be pre-selected for monitoring). Whether the potential for human health or ecological effects from this subset of PPCPs is eventually demonstrated is in large part irrelevant. More important, these occurrence data demonstrate the potential for ANY consumer-use chemical to enter the environment. This foresight advances us the opportunity to be watchful regarding the future introduction to commerce of drugs possessing totally new mechanisms of action and ever-increasing biochemical potencies.

Drug usage can be expected to continue to expand and increase because of a confluence of drivers: increased per capita consumption, expanding population, expanding potential markets (partly due to mainstream advertising/marketing), patent expirations (shift to less expensive generics), new target age groups, inverting age structure in the general population, and new uses for existing drugs. Old therapeutics are being used not just for additional clinical conditions (those for which they were not originally developed) but also for non-disease states — for example, medical manipulation or alteration of personality traits and satisfaction of certain social needs — referred to as "cosmetic pharmacology."

Limitations of Guidelines for Performing Environmental Risk Assessments: Our ability to assess the risks (if any) that might be posed to ecological or human health by PPCPs in the environment is greatly hampered by the profound lack of relevant toxicological information, especially for the aquatic environment, which tends to be the ultimate sink for these rather non-volatile, amphiphilic compounds (although terrestrial exposure can occur when sewage sludge with sorbed or occluded PPCPs is applied to

land) (see: Daughton and Ternes 1999; NRC 2002b). For example, in the U.S., environmental assessments for approving NDAs (new drug applications) are required by the U.S. FDA only when the concentration of a drug predicted to enter the aquatic environment (expected environmental concentration, EEC; or predicted environmental concentration, PEC, as used in Europe) would be 1 µg/L (1 ppb) or greater (USDHHS 1998). FDA's historical toxicity data for standard aquatic tests demonstrate no conventional effects at concentrations less than 1 ppb; also see regulatory discussions by Velagaleti and coauthors (Velagaleti and Gill 2001; Velagaleti et al. 2002). In contrast, the European Agency for the Evaluation of Medicinal Products (EMEA 2001) has proposed a trigger value of 0.01 µg/L (10 ppt) (see discussion by Straub 2002). Regardless of the actual value, however, the scientific validity of these trigger approaches has been questioned (e.g., see: CSTEE 2001), an issue stemming primarily from the dearth of toxicological information on non-target species. Regardless of whether trigger values may be used, there are three major additional factors that are not accounted for in any approach that uses "predicted" environmental concentrations (i.e., EEC or PEC).

(1) Ramifications of Geographic Variability in Drug Usage. Calculation of predicted environmental concentrations assumes a uniform geographic usage. In practice, however, environmental occurrence is a function of local prescribing practices and usage customs and confluence of hospitals (whose usage of drug types differs from the general community). While PPCP production/usage figures are largely confidential, recent data from the first-ever study published on geographic variation (across the U.S.) of prescription drug usage (Express Scripts 2001) shows that at least for some drugs, regional preferences in usage can vary by several fold or more. The types of drugs (and dosages) can vary significantly from municipality to municipality, county to county, region to region, and from country to country — largely as a function of age structure of the populations and prescribing customs. This means that for highly populated metropolitan areas with usage of a particular drug exceeding what would be expected by a

uniform distribution, the actual environmental concentration (EEC or PEC) could be higher than predicted.

(2) Unaccounted Sources: There are also a variety of largely undetectable, alternate sources for PPCPs (other than legal sales through approved market channels) that contribute to overall usage and which are not accounted for in EEC or PEC calculations. Further complicating matters is that prescription numbers and OTC (over-the-counter) sales are only a rough measure of a drug's usage because they account for only a portion of the overall use. Physician samples (drugs that are not intended to be sold but rather intended to promote the sale of a drug), the resale "diversion market", black market sales, free trial offers by manufacturers, and the little-publicized "prescription drug patient assistance programs" sponsored by the pharmaceutical industry (e.g., see links at: DisabilityResources.org 2002) are other, perhaps substantial, sources that are difficult to account for. As an example, the sales of drugs via the Internet may incur a substantial, unregulated import of unknown quantities of drugs from foreign countries; Internet sales continue to increase and as such pose a concern to the U.S. FDA (2002a) in terms of consumer health. Countries also vary as to whether a drug is available by prescription only or via OTC (this could be significant for those drugs that have the potential to be transported across geographic boundaries).

(3) Interactions. Exposure to but one solitary toxicant at a time is most likely an extraordinarily rare event, especially in the aquatic domain. Exposure is more likely a routine multidimensional occurrence involving multiple chemical stressors with dynamic spatial and temporal components and whose outcomes have a strong dependency on prior exposure history (described earlier, in the "Introduction" as the "4T's"). The current practice of risk assessment considers a single stressor at a time, and if the predicted environmental concentration for the single stressor is below the "no effect concentration" (which is a direct reflection solely of the select few of the countless endpoints that happen to be selected),

further assessment is usually deemed as unnecessary. This approach clearly relies on stressors acting in sequence and independently (i.e., no interactions); but aggregate and cumulative exposure may play significant roles (see Fig. 2) .

In the final analysis, maximum predicted environmental concentrations should eventually be corroborated through more extensive monitoring of all relevant environmental compartments — the only way to verify whether predicted concentrations comport with reality. One way to collect sufficient data would be through a program such as the U.S. EPA Office of Water's Drinking Water Contaminant Candidate List (CCL), which is administered under the EPA's "Unregulated Contaminant Monitoring Rule" (U.S. EPA Office of Water 2002).

SOURCES: PPCPs in the Environment and Their Control

From the patterns that have emerged in the published occurrence data, it is now clear that ALL municipal treated sewage (unless subjected to advanced wastewater treatment technologies such as reverse osmosis and granular activated carbon) — regardless of location — will contain PPCPs. The issue is not unique to any particular municipal area. Each geographic area will differ only with respect to the types, quantities, and relative abundances of individual PPCPs. There are a number of major sources contributing to the introduction of both licit and illicit drugs to the environment (see summary: Daughton/EPA 2002c). The major three are probably excretion, washing, and purposeful disposal. These three sources most likely feed into municipal waste systems and storm run off (e.g., sanitary or combined sewers), and to a lesser but significant degree are discharged directly to surface waters via "straight-piping." Waste discharged to engineered systems is subjected to various levels of treatment-technology sophistication prior to discharge to receiving waters. PPCPs, however, display a broad range of removal efficiencies by waste and water treatment technologies; some travel through sewage treatment facilities with only minor reductions in concentration (the antiepileptic carbamazepine is but one example) (Daughton and Ternes 1999; Heberer 2002). There are also some minor overall sources that could potentially play significantly large local roles. One is cemeteries, which could provide a source of PPCPs to the subsurface (see section: "Environmentally Sound Funeral Practices," under "Drug Disposal/Recycling/Pollution Prevention" in Part II [Daughton 2003b]).

The continual input of PPCPs to the aquatic environment via sewage can impart a persistence-like quality to those compounds that otherwise possess little inherent chemical stability in the environment (Daughton and Ternes 1999) because it serves to replenish those that are being removed; these chemicals can be referred to as "pseudo-persistent" pollutants (Daughton 2002a). The full extent, magnitude, and ramifications of their presence in the aquatic environment, however, are largely unknown. The two largest

unknown domains in toxicology, and which are centrally germane to PPCPs as environmental pollutants are the significance of: (1) chronic, multi-generational, low-dose exposure (i.e., nM-pM [sub-ppb/ppt], a common concentration range for PPCPs in waters) and (2) simultaneous exposure to multiple stressors. Both of these are further complicated by the added dimension of each chemical perhaps being in a constant state of flux in both absolute and relative abundance. The occurrence differences of PPCPs in raw sewage are a function of: (i) local prescribing and usage customs, (ii) confluence of hospitals, (iii) state policies and customs regarding disposal of unused PPCPs, and (iv) local manufacture and usage of illicit and abused drugs. For surface and ground waters, the differences are a function of: (i) whether any treatment technologies are employed (straight-piping, malfunctioning septic systems, overflow events), (ii) types of treatment technologies employed for sewage, potable water, or reinjection waters, and (iii) local/seasonal fluctuations in biophysicochemical transformation potential (e.g., biodegradation, photolysis, sediment/particulate sequestration).

Key Importance of Water Resources — Impact of Untreated Sewage: Regardless of whether the efficiencies of waste or drinking water treatment approaches can be improved, large volumes of untreated wastewaters are discharged to surface waters each year. The release of PPCPs into the environment would be maximized by the release of raw sewage. Sources of raw sewage in the U.S. released to streams, lakes, estuaries, oceans, groundwater are responsible for high but largely unknown volumes: (i) combined sewer overflows (CSOs) contribute over 4×10^{12} L/year (CSOs handle rainwater runoff, domestic sewage, and industrial wastewater, and are designed to discharge untreated sewage during adverse storm events; U.S. EPA Office of Wastewater Management (2002a); (ii) sanitary sewer overflows (SSOs) (severe weather, system malfunction, improper system operation/maintenance); (iii) leakage from sewage transport infrastructure (sewer pipe cracks caused by tree roots and defective/collapsed pipes); (iv) failing septic systems; (v) unpermitted privies; and (vi) straight-piping.

Repair of existing sewage and water handling infrastructure in the U.S. will require huge resources. The American Society of Civil Engineers *2001 Report Card for America's Infrastructure* (ASCE 2001) assigned nationwide grades of "D" for both drinking water and wastewater infrastructures. Over $20 billion annually is the estimated need for rectifying the nation's degenerating water/waste infrastructures.

If PPCPs eventually prove to be an environmental concern, it is unknown whether sewage treatment facilities could even be cost-effectively modified to reduce emissions — especially given the huge costs associated with re-establishing and maintaining their original performance. Ultimately, source control (pollution prevention) aimed at disposal practices as well as actual therapeutic usage may prove more effective. The remainder of this paper (Part I) and all of Part II (Daughton 2003b) present ideas regarding the broad spectrum of activities that could be encompassed by pollution prevention.

POLLUTION PREVENTION

Regardless of the outcome of the toxicological significance of PPCPs for ecological systems (including humans), and regardless of the progress that can be made with respect to improving waste or water treatment technologies, a wide variety of actions can be initiated in the near term to minimize the introduction of PPCPs (as well as other consumer-oriented xenobiotics) to the environment and thereby reduce the potential for emerging risks or risks that have yet to be gauged or characterized. These proactive actions span a wide spectrum of disciplines and serve as the focus for this two-part paper, a focus that is driven by four of the 10 goals that formed the basis of U.S. EPA's 2000 Strategic Plan — Goal 2 (Clean and Safe Water), Goal 4 (Preventing Pollution and Reducing Risk in Communities, Homes, Workplaces, and Ecosystems), Goal 5 (Better Waste Management, Restoration of Contaminated Waste Sites, and Emergency Response), and Goal 8 (Sound Science - Improved Understanding of Environmental Risk, and Greater Innovation to Address Environmental Problems) (see: U.S. EPA 2000). In addition, one of the primary goals of the U.S. EPA's Office of Research and Development is to identify

and foster investigation of previously "hidden" or potential environmental issues/concerns before they become critical ecological or human health problems — pollution prevention (e.g., source elimination or minimization) being preferable to remediation or restoration (so as to minimize both public cost and human/ecological exposure).

Collateral Benefits: An important consequence of reducing the introduction of PPCPs to the environment is that a wide range of other benefits could accrue to both consumers and to industry. By addressing the environmental issues associated with PPCPs as environmental contaminants, in most respects substantial collateral improvements to healthcare could also be achieved. These are highlighted in various sections of both Parts I and II of this paper. Benefits to consumers could include reduced health care costs partly as a result of a more efficient and safe administration of all chemicals used in health care.

ENVIRONMENTAL SURPRISE and the PRECAUTIONARY PRINCIPLE

A proactive approach to dealing with issues posing unknown or unpredictable consequence is rooted in the concept of "surprise" in environmental systems. This concept was perhaps originally formalized by the ecologist Crawford S. (Buzz) Holling in the early 1970s. "Surprise" occurs when "... causes turn out to be sharply different than was conceived, when behaviors are profoundly unexpected, and when action produces a result opposite to that intended - in short, when perceived reality departs *qualitatively* from expectation." (Holling 1986, p. 294). Environmental surprise is where the ultimate hazards may differ from those that were anticipated. Further discussion is provided by Schneider and Turner (1994).

In Holling's view, "resilience" may enable an ecosystem to return to a steady state after being subjected to an unusual event (or an ongoing succession of cumulative events) denoted as being a "surprise". But the

state to which it reverts may be different — in other words, a discontinuous change is effected. The ramifications of subtle perturbations to complex systems such as ecosystems have been discussed in many forums (sometimes under the moniker of the "butterfly effect," where the flapping of a butterfly's wings in one geographic locale may make the difference sometime in the future between calm and unstable weather in another locale; Gleick 1987). Lorenz concluded that the sensitivity to initial conditions "implies that two states differing by imperceptible amounts may eventually evolve into two considerably different states. If, then, there is any error whatever in observing the present state - and in any real system such errors seem inevitable - an acceptable prediction of an instantaneous state in the distant future may well be impossible" (p. 133) (Lorenz 1963). Minuscule differences in initial conditions can lead to differences far out of proportion in the system's subsequent behavior. In this sense, minor perturbations can essentially be slowly amplified to yield major effects. This was a theme espoused by Daughton and Ternes (1999) and by Daughton (2001a) — namely, subtle, cumulative effects, largely undistinguishable from natural change, eventually culminating in profound change. Ths same idea has been elaborated upon by Thornton (2000); this concept has parallels with the idea of "the tyranny of small decisions" or what Odum refers to as "small decision effects" — major unforeseen outcomes resulting from a "multitude of small pin pricks" (Odum 1982). Moreover, it may not be possible to detect subtle changes in systems so complex (such as ecosystems) that their intricately interwoven processes are poorly understood to begin with. This paradox is further complexified by our inability to distinguish what we might refer to as a "normal" functioning of a complex system from abnormal. If the basis for comparison is an already affected system (albeit unrecognized as such), then further detection of any change can be impaired or obscured.

Proportionality between cause and effect, while a tenet of single-organism-based toxicology, does not necessarily hold for higher levels of organization such as communities or ecosystems because of the myriads of interactions and spatial relationships within the system — some imparting vulnerability to

synergistic effects. When perturbations exceed the resilience of a system, irreversible change can occur. Ecological systems inherit information (cumulative effects) through time (part of the 4T's), their complex interlinkages affect one another synergistically, and their continually changing complexity makes them vulnerable to irreversible change. These ideas are formalized in the "Community Conditioning Hypothesis" (Landis 2002), where the etiology of each ecological structure evolves from a unique trajectory. This hypothesis holds that any predictions are rife with uncertainty, but that most stressors leave lasting signatures, and stressors can "act from a distance" (p. 197).

Most recently, the philosophy that all systems self-organize in perpetual imbalance (cusps or knife-edges of instability, poised at the edge of chaos), as synthesized by Buchanan (2001) around nonequilibrium physics, further consolidates the idea that small events can trigger disproportionately large responses that are not predictable — cause and effect are not linked in certainty, but rather in surprise. Response is more a function of the composite *history* of the system rather than its snap-shot status (the concept of "historical physics" as opposed to equilibrium physics). With these thoughts in mind, evidence continues to accumulate that while it may never be possible to gage humanity's contribution to adverse environmental or human health events or outcomes, it might behoove us to eliminate as many extraneous variables (impacts) in ecosystems as possible — regardless of their perceived immediate importance.

The idea of unexpected change from perturbation of ecological systems is one of the driving forces behind the *Precautionary Principle*. When applied to assessing risks associated with chemicals as pollutants, the principle of precautionary action redistributes the burden of proof because the science required for truly and fully assessing risks lags far behind that which is needed. For some comprehensive discussions on the Precautionary Principle (also known as the principle of "reverse onus"), refer to the links at Daughton/EPA (2002d). Science, in the face of uncertainty, must be melded with policy and political judgment to arrive at a course of further study or action. Many environmental issues, given their

extreme complexity and the assurance that a thorough understanding of any isolated aspect (no less a truly needed, overarching systems-level, holistic understanding) may occur only far in the future, will require an approach based on an unorthodox, dichotomous mixture of subjective (and at times emotional) values wedded to reasoned, science-based logic; this point relates to the reasons for the difficulties associated with how science measures "real" hazard versus how society actually perceives risk (a topic thoroughly addressed in a broad body of work by Paul Slovic and others; for an example, see: Slovic 2001). A recent compilation of case histories shows how the Precautionary Principle did serve (or could have served) in a variety of situations (Harremoës et al. 2001).

To illustrate that chemicals can have unforeseen, subtle effects, consider atrazine, a herbicide used widely and heavily for about 40 years and for which perhaps thousands of published investigations had repeatedly verified a dearth of adverse effects on aquatic non-target organisms at the tens of parts-per-billion range. The recent report (Hayes et al. 2002) of atrazine possibly modulating aromatase in the African clawed frog (*Xenopus laevis*), and perhaps explaining the alteration in sexual development at sub-ppb levels, points to the need for more attention to "subtle" effects (Daughton and Ternes 1999).

The Precautionary Principle has a long and still extremely controversial history. Its adoption by Europe, Canada, and the U.S. has proved extraordinarily uneven, influenced largely by differences in cultural and political histories and imperatives. But regardless of the heated debate surrounding the Precautionary Principle, deep-rooted fundamental changes in corporate philosophies are beginning to emerge in the way that environmental considerations are melded with market imperatives — the two are beginning to merge as it becomes apparent that many economic advantages (and seemingly unrelated, and often unforeseen, societal advantages) can be gained by employing environmental stewardship as a foundation for corporate philosophy. A proactive, voluntary holistic stewardship program for PPCPs (first alluded to by Daughton 2002a) would also be preferable to a reactive, prescriptive regulatory program. By focusing on

developing a mind set toward holistic, thoughtful environmental responsibility, rather than rote compliance to regulations, all aspects of society can play integral roles. This approach is also in keeping with EPA's new Innovation Strategy (Gibson 2002; U.S. EPA 2002). Indeed, avoiding the syndrome of insidious, cumulative environmental degradation by way of "small decision effects" ("multitude of small pin pricks") may be possible only in embracing a holistic view of the world around us (Odum 1982).

The fusion of ecological and marketplace imperatives has perhaps emerged most noticeably in the relatively recent product management philosophy termed "cradle-to cradle" (see below: "Cradle-to-Cradle Stewardship") — in contrast to the "cradle-to-grave" approach that has long been the objective of recycling.

WATER QUALITY — KEY TO MANY DOORS IN THE 21st CENTURY

The growing, cardinal importance of water for sustaining societies is becoming more widely recognized as recently evidenced by its central role in the Broadway musical "Urinetown" (2002). The story is set at a time when "water is worth its very weight in gold." "A depletion of the earth's water supply has led to a government enforced ban on private toilets. The privilege to pee is regulated by a single, malevolent corporation, which profits by charging admission for one of mankind's most basic needs."

A backdrop to the Precautionary Principle is the growing imperative for water re-use, which will prove to be the key, critical driving force for management of water quality in the 21st century. The National Research Council (as requested by the National Science Foundation, NRC 2001) synthesized the broad expertise from across the many disciplines embodied in environmental science to offer its judgment as to the most significant environmental research challenges of the next generation — based on their "potential to provide a scientific breakthrough of practical importance to humankind if given major new funding".

Of the eight "grand challenges" identified in the NRC's report, two involve water quality issues, both relevant to PPCPs: (1) "Hydrologic Forecasting" (for predicting changes in freshwater resources as a result in part of chemical contamination) and (2) "Reinventing the Use of Materials". The impetus driving the second is "new compounds and other substances are constantly being incorporated into modern technology and hence into the environment, with insufficient thought being given to the implications of these actions. All of these issues assume added importance in urban areas, which concentrate flows of resources, generation of residues, and environmental impacts within spatially constrained areas. From a policy standpoint, reliable predictive models of material cycles could be invaluable in guiding decisions about ... topics relating to human-environment interactions..." (p. 55) "This grand challenge centrally encompasses questions about societal-level consumption patterns, since consumption is the primary force driving human perturbations of material cycles." (p. 55).

Likewise, the World Health Organization's *World Water Day Report* draws international attention to the intimate connection between water and health: "Due to a mix of geographical, environmental and financial factors, as well as to increased pollution from municipal and industrial waste, the leaching of fertilizers and pesticides used in agriculture, only about one-third of the world's potential fresh water can be used for human needs. As pollution increases, the amount of usable water decreases." (p. 7, Chapter 1, WHO 2001); links to numerous resources regarding freshwater can be found at The World's Water (2002). The concept of the "Ecological Footprint" (Wackernagel and Rees 1995) also highlights the central importance of water. Residents of industrialized countries may need an average of 10-22 acres per capita to support an urban lifestyle. One of the major issues facing water resource managers in the 21st century will be to understand the overall impact of the urban ecological "footprint" on water resources. While there are numerous consequences of the footprint, a major concern may be the continued use of urban waterways as "waste receptacles" — merely for diluting and transporting downstream the by-products of urban consumption.

While the emphasis of this background material is on the aquatic environment, it is important to not lose sight of the other environmental compartments with which PPCPs can interact. The most significant of these secondary concerns is sewage sludge, to which certain PPCPs can sorb or partition. Subsequent application of sewage sludge ("biosolids") to land (for example as a soil amendment) holds the potential for exposure of terrestrial ecosystems. The National Research Council (NRC) revisited the issue of biosolids (NRC 2002b; see in particular chapters 5 and 6) with respect to reevaluating the approach used by the EPA in setting its chemical standards for the "Biosolids Rule" (U.S. EPA Office of Wastewater Management 2002b). The NRC recommended that "... a research program be developed for pharmaceuticals and other chemicals likely to be present in biosolids that are not currently included in routine monitoring programs." The NRC also recommended that alternative (i.e., non-traditional) toxic endpoints be considered.

HEALTH OF ECOLOGY versus ECOLOGY OF HEALTH

The intimate, inseparable connections between humans and the environment (actually, humans can be viewed as an integral *part* of the environment) have been widely discussed in many contexts. By applying principles of medicine and public health to the environment, David Rapport formalized the concepts of "ecological health" and "ecosystem medicine" (Rapport 2002). The "health of ecology" refers to ecosystem health. The "ecology of health" refers to human health as being determined in part by the condition of ecology (creation and transmission of antibiotic resistance is but one example). Ecological stress is reflected by stress in humans — the two are intimately tied; a gradual awakening to the interconnections that have always existed but which have been largely masked by science's historic propensity toward reductionism is witnessed by a number of articles (e.g., one of the more recent books by Di Giulio and Benson 2002) as well as by a growing interest in holistic "systems biology" (e.g., Oltvai and Barabási 2002). Adverse effects in one are eventually reflected in the other. The Institute of Medicine

(IOM) has called for a revolution is re-engineering all aspects of the healthcare system in the U.S. A major objective of the IOM Quality of Health Care in America Committee (formed in June 1998) was to develop a national strategy to radically improve the quality of U.S. healthcare within 10 years. To date, their recommendations (e.g., see IOM 2000, 2001) address the many aspects of patient safety and how the concepts of quality systems can be applied. While the IOM's goals are far-reaching and urgently needed, they do not include the concept of ecology of the health. Safety of the patient is pursued out of context of the safety of the ecology. With a little expansion of the IOM vision, an integration of human and ecological health could be formalized at a national level through their efforts. High quality health care and environmental protection need not be competing goals — they are intimately linked.

Connecting Health of Ecology and Human Health: Health Promotion & Social Entrepreneurs: The specific environmental issues and the example solutions posed in this paper are not as pertinent to those parts of the world where PPCPs are little-used, such as economically disadvantaged regions (except in those areas where large-scale drug-disposal occurs, such as from humanitarian operations; e.g., WHO 1999) or where illicit drug manufacturing or use is prevalent (Daughton 2001c). But nonetheless, the basic, universal concept of a "health state" (rather than an "absence of illness"), being one of a balanced and interconnected physical, mental, social, and spiritual well-being, is equally applicable to Western cultures and could have a profound impact on overall drug usage (both licit and illicit). Treatment of physiological and psychological symptoms and even the curing of diseases compose but one dimension of holistic health - - and in many respects, preventive and curative approaches are but stop-gap measures in the absence of a sustainable environment. As an example, the argument can be made that the single most important limitation in the continual quest to eliminate infectious diseases is not the lack of medication, but rather the failure to address poverty and its attendant liabilities of hygiene and malnutrition.

Many people actively engaged in advancing the principles of "sustainability" (sometimes defined as meeting society's needs in ways not diminishing the capacity of future generations to meet theirs) have strongly felt that without empowering people to take charge of the basic aspects of their own lives, sustainable improvements in health are not possible. A model effort (Comprehensive Rural Health Project) begun in 1970 by the Indian medical doctors Drs. Raj Arole and Mabelle Arole (his late wife) has demonstrated how a holistic approach builds a foundation for sustainable living and only then is advancement in improving health possible. Health cannot be dissociated from all the other aspects of sustainable living (Arole 2001); the burgeoning field of "sustainability" is captured by the ISTS (2002), among others. Social entrepreneur projects in "health promotion" (in contrast to illness/disease prevention), such as those begun by the Arole's, abandon narrow technical objectives aimed at preventative and curative measures in pursuit of wider-ranging holistic goals that emphasize the interconnectedness of social systems.

CRADLE-TO-CRADLE STEWARDSHIP

Guided by the inter-relationships between the Precautionary Principle, the ever-increasing and key worldwide importance of water, and the idea of "ecology of health," the incorporation of "eco-effectiveness," "ecological intelligence," or "cradle-to-cradle" design concepts into life-cycle considerations for product development and use has gained momentum in the last decade. The idea of cradle-to-cradle stewardship has most recently been embraced by a number of international corporations. Some of the more visible and successful proponents of cradle-to-cradle concepts have been William McDonough and Michael Braungart (see McDonough and Braungart 2002; MBDC 2002). They have been leaders in implementing the idea of full life-cycle product design, referring to this approach as the "Next Industrial Revolution". One of the tenets of this philosophy for a truly sustainable industry is that it benefit not just the environment, but also the consumer and corporation alike; this is one reason for the expression sometimes used for these programs — "waste to wealth". Numerous other similar efforts have

been successfully underway; examples include those with monikers such as "Zero-Waste" and "Zero Emissions," being implemented in Canada by the Recycling Council of British Columbia (RCBC 2002). Another effort toward directing organizations toward sustainability is being led by the international organization "The Natural Step" (TNS 2002). Of the "Four System Conditions" that The Natural Step framework is based upon, the second states: "In a sustainable society, nature is not subject to systematically increasing concentrations of substances produced by society." It is worth noting from an historical perspective, however, that the idea of sustainability was put forth decades ago, as early as 1966 (Blutstein 2003).

UNEP (2002) notes that while significant efforts in reducing environmental footprints have been made by a few companies across many industrial sectors, a gap continues to widen between these few and the vast majority that continue with "doing business as usual". Among the five major areas for advancement toward true sustainability identified by UNEP (2002), the fourth is the "integration of social, environmental and economic issues." These efforts hint that a sustained future viability of this product life-cycle philosophy can be expected. A wide range of strategies that could foster a cradle-to-cradle approach for stewardship of PPCPs by the pharmaceutical/medical care industries could be adopted. Some could be implemented quickly (requiring only a collective will to implement them); others would require sustained R&D efforts (which in some cases are already underway, albeit for reasons unrelated to environmental benefits), and some would require major attention by the numerous agencies involved with a patchwork of laws and regulation of drug recycling and disposal. A number of examples are outlined in various sections of this paper and its companion piece, Part II (Daughton 2003b).

VIABLE OPTIONS FOR MINIMIZING THE INTRODUCTION OF PPCPs TO THE ENVIRONMENT

Numerous actions could be implemented in the near-term for reducing what risks might exist from introducing PPCPs to the environment. In the longer term, a number of research avenues could be pursued regarding drug design, packaging, and delivery — all of which could provide environmental (as well as consumer) pay-backs. Indeed, some of these are already being pursued. Many would yield direct benefits to human health for a variety of reasons unrelated to any environmental imperative, including reduction of inappropriate drug usage and lowering of therapeutic dosages (thereby lessening adverse drug reactions and reducing consumer costs).

It should be noted that a number of pharmaceutical producers and organizations have "product stewardship" as an integral part of their business. These programs, however, while sometimes acknowledging the issues associated with consumer-use of PPCPs, tend to focus on the aspects of the manufacturing process (as opposed to distribution and usage) as well as on hospital waste (see examples at: Daughton/EPA 2002e). A potential mechanism for effecting change in the health-care industry (starting with hospitals) is via an existing program established under a program agreed to in 1998 by the American Hospital Association (AHA) and the U. S. EPA and administered by the Hospitals for a Healthy Environment (H2E 2002). This program's overall goal is to reduce the impact of health care facilities on the environment. While initially focused on the elimination of mercury and reduction of total waste volume, a future area of consideration is development of model chemical waste minimization plans ("AModel Plans").

Some of the ideas presented below may prove controversial. They are being highlighted solely with the objective that doing so will generate an active dialog or debate across the many disciplines that must

become involved to successfully address this topic. Many of these disciplines have never before had any reason to interact or collaborate with each other. With the increasing visibility of PPCPs as pollutants, it is now hoped that these disparate professional communities will find compelling reasons to cross-communicate, and in doing so, expand their knowledge and effectiveness in their own fields.

AVENUES FOR PROGRESS TOWARD A "GREEN PHARMACY"

Over the last decade, tremendous progress has been made in advancing the practice of "green chemistry" (e.g., minimizing the use of ecologically hazardous reagents and designing alternate synthesis pathways, some of which are based on aqueous chemistry) (U.S. EPA Office of Pollution Prevention and Toxics 2002). In fact, the pharmaceutical industry has a strong history in applying environmentally responsible chemistry (which also turns out to be economically advantageous) to drug synthesis and manufacturing. The same principles could be logically extended and applied to drug design, delivery, package design, dispensing, and disposal so that their benefits could accrue to the end user and not just the manufacturer. Some of these ideas for minimizing the release of PPCPs to the environment have already been put forth (see: Daughton and Ternes 1999) but will be reiterated and expanded on here because they have never been brought together in one document. Unfortunately, despite the many avenues of advancement that could be — and sometimes already are already being — made toward a green healthcare system, the transfer of new knowledge and technology to clinical practice is notoriously slow; as one example, new knowledge gained from clinical trials takes an average of 17 years to become incorporated into routine practice (IOM 2001).

DRUG DESIGN: New drug design (chemical structure and properties) and formulation (combination of the active, therapeutic ingredient with the "inert," non-active ingredients known as "excipients") should factor in new considerations for "environmental friendliness" or "environmental proclivity". Such

"green" PPCPs would maintain or improve therapeutic or cosmetic efficacy while also maximizing their susceptibility to biodegradation, photolysis, or other physicochemical alterations to yield innocuous end products. Design of more labile drugs (e.g., those that would ordinarily be degraded by, or poorly transported across, the gut) would further reduce excretion. Current drugs that do undergo initial structural alterations (e.g., via phase I or phase II metabolism) tend to often yield broad arrays of metabolites, some of which are the actual active drug form and some of which are environmentally persistent; in light of what little is known regarding effects to non-target species by parent drugs, even less is known about metabolites. Drugs could be designed with better physiological sorption characteristics (to lessen direct excretion of the parent compound). Using smaller doses by enhancing the delivery exclusively to the target site or receptor is an objective being pursued on many fronts, including better drug design to accommodate existing membrane transporters (e.g., XenoPort 2002) as well as "creating" in-situ synthetic transporters (see summary at: Alper 2002). Sometimes the formulation of a drug can impede its sorption, especially for those with ill health or impaired gastrointestinal function; rapid-dissolve tablets are one example of an improvement over formulations that can impede or prevent dissolution; for example, the common excipient stearic acid often impedes dissolution (Daughton 2001a). New formulations are particularly needed for insoluble drugs (about 30% of USP drugs and 50% of prospective drugs are poorly water-soluble); current examples include liposomal delivery, polymer-drug conjugate prodrugs (with release at the target site), and special formulating approaches, such as Insoluble Drug Delivery (RTP Pharma 2002). Other examples include novel targeting approaches, such as patient re-infusion of autologous erythrocytes that have been altered to encapsulate drugs, permitting a steady, low-drug concentration to be attained for a period of weeks and which can selectively target certain sites such as macrophages (Magnani et al. 2002).

The Future of Omics: While the rapidly advancing "Omics" revolution (genomics, proteomics, glycomics, metabolomics, etc.; see: CHI 2002) will probably lead to the development of countless new

classes of drugs (some with mechanisms of action never-before-encountered by any organism, and therefore posing the attendant questions as to the possibilities for previously unconsidered effects on non-target organisms), at the same time, identification of genetic idiosyncracies will allow the selective targeting of specific sub-populations of patients for treatment with these same new drugs — thereby allowing for their reduced usage across the larger population. "Pharmacogenomics" holds great promise to both (i) greatly increase the numbers of low-usage drugs (those specifically tailored to narrowly defined patient populations, effectively vastly increasing the number of therapeutic niches), as well as (ii) increase the numbers of high-usage ("block-buster") drugs (by addressing therapeutic targets of minimal genetic variability across the population to yield drugs of extremely broad tolerability). By increasing the efficiency of drug discovery (minimizing failures), the reduced costs will in turn catalyze yet more new-drug discovery. "Genomics" is also recognized by the U.S. EPA as providing new opportunities for risk assessment and predictive toxicology, and as such will continue to gain new applications (U.S. EPA Science Policy Council 2002).

Dirty Drugs to Designer Drugs: With better-designed drugs (as opposed to those with a broad spectrum of molecular actions — "dirty" or "promiscuous" drugs), by increasing the specificity of drug action at the target receptor, not only could adverse reactions be minimized, but with extremely narrow MOAs, it would also prove easier to predict the potential for effects on non-target species. Another example (with regard to drug discovery/design) is the development of drugs with higher potency (and therefore lower doses) as a result of greater systemic availability. Drug potency is partially a function of absorption efficiency (lower doses necessitated by higher absorption efficiency). Recently, as reported by Veber et al. (2002), reduced molecular flexibility (as measured by the number of rotatable bonds) coupled with lower polar surface area (or total hydrogen bond count) was shown to reflect good oral bioavailability — independent of low-molecular weight or lipophilicity, as long held by "Lipinski's Rule of Five". Absorption had been thought to be a strict function of molecular weight (e.g., MW>500 led to

poor absorption; low MW was required for good systemic availability). At least in rats, however, Veber et al. (2002) show that it is not necessarily MW, but rather the rigidity of the molecule (which is partly an indirect function of MW) that is a prime determinant. This points to the possibility that higher-molecular weight drugs for humans are possible as long as the number of rotatable bonds is minimized. For rats, the more rigid molecules (those with 10 or fewer rotatable bonds and lower polar surface area) show the better oral absorption; lowest absorption occurs with those having more than 10 ("flexible" compounds). The "Rule of Five" (Lipinski 2002; Lipinski et al. 1997) as a predictor of oral bioavailability posits that either the number 5 or a multiple of 5 was involved in the predictive parameters (but there were only 4 rules in the "rule of five"): "In the discovery setting 'the rule of 5' predicts that poor absorption or permeation is more likely when there are more than ***5*** H-bond donors, ***10*** H-bond acceptors, the molecular weight ... is greater than ***500*** and the calculated Log P ... is greater than ***5***..." (emphasis added). The number of rotatable bonds (Veber et al. 2002) would add the fifth rule.

Chirality's Role: Design that lessens therapeutic doses without increasing overall potency is already occurring with the emphasis on enantiomerically pure drugs (homo-chiral drugs), which can have therapeutic advantages over their conventional racemic mixtures. One of the first commercial examples was (R)-albuterol or levalbuterol (Xopenex), the homo-chiral version of racemic albuterol, where broncodilation could be achieved with levalbuterol at one-fourth the dose of racemic albuterol (and with fewer side effects) (Handley et al. 2000); a more recent example is esomeprazole (Nexium), the homo-chiral form of omeprazole (Prilosec). This approach not only cuts the overall dose by at least one-half (sometimes more, depending on the number of isomers) and totally eliminates exposure to the other (non-therapeutic) isomer(s), which frequently has completely different mechanisms of action, it can also yield benefits to the patient by removal of non-therapeutic isomers that were also responsible for unwanted side effects. The commercial-scale production of homo-chiral drugs, however, is fraught with scale-up difficulties; advances in economic racemic separation efficiencies will prove useful (e.g., see: Lee et al.

2002). The development of enantiomerically pure drugs to reduce environmental loadings has a parallel with pesticides. Optically pure pesticides have been approved by the EPA (e.g., S-metolachlor) under the EPA's Reduced Risk Pesticide initiative (under the Food Quality Protection Act, FQPA) (U.S. EPA Office of Pesticide Programs 1996). For metolachlor, this would possibly serve to lessen its overall use by 35%.

Emulating Nature: Another design strategy would be "smart" drugs that better emulate the non-anthropocentric, native chemistries of natural products. As examples, consider (i) the newer classes of antimicrobial peptides modeled after the endogenous antimicrobials (e.g., defensins, piscidins, and cathelicidins — "caths"; Toma 2001), (ii) bacteriophages (viruses that infect only bacteria; e.g., see: Intralytix 2002), and (iii) the enzymes used by phages to destroy their bacterial hosts (e.g., highly species-specific lysins); indeed "phage therapy" using live bacteriophages enjoyed large-scale success as first employed by Soviet microbiologists beginning in the 1920s (Stone 2002). One new approach uses synthetic cyclic peptides (some with the non-native optical isomers) to disrupt cell wall/membrane function or physical integrity (Fernandez-Lopez et al. 2002). While naturally produced antimicrobials and analogs may not be sufficient on their own, their use could serve to potentiate the action of existing synthetic antibiotics and thereby reduce overall usage. These natural products could also reduce overall antibiotic usage by prophylactic use — in preventing the onset of infection. Another example is the synthetic musk fragrances. The two classes that have been used extensively are the nitro musks and the polycyclic musks. Certain members of these classes (or their metabolites) are known to persist and bioaccumulate (see references cited: Daughton and Ternes 1999; Daughton 2001a). A third class that is not used as extensively because of its cost comprises the macrocyclic musks (15-18 carbon cycles closed as either a carbonyl or lactone), which better emulate natural musks and are purportedly more biodegradable.

Avenues to Resurrection: "Resurrection" of "retired" drugs that are no longer efficacious (for example, because of development of pervasive pathogen or tumor resistance) could allow for the continued use of older-generation drugs that could be more environmentally friendly. Resurrection could be accomplished by developing potentiators that are not inherently toxic but which overcome, for example, the defensive strategies used by resistant target organisms or tissues. An example is the development of multi-drug efflux pump inhibitors (EPIs) (see discussion in: Daughton and Ternes 1999). One (of many) example class of existing EPIs are certain SSRI antidepressants (Munoz-Bellido et al. 2000), which have been shown to synergize the activity of some antibiotics. But strategies designed to counteract general defensive strategies (such as efflux pumps) need to be carefully assessed in light of their potential for compromising the health of non-target species, many of which (esp. in the aquatic realm) employ efflux pumps as a first line of defense against toxicants (see Daughton and Ternes 1999; Daughton 2001a; Epel and Smital 2001).

Alternative Medicines Missing from the Radar: The World Health Organization (WHO) developed a strategy for addressing issues of policy, safety, efficacy, quality, access, knowledge preservation/protection, and rational use of "traditional, complementary, and alternative medicine" (TM/CAM) (WHO 2002b). That WHO put forth this first global strategy clearly signals that TM/CAM has gained substantial stature. The popularity of TM/CAM in less developed countries is widely appreciated; its growth in more developed countries over the last couple decades is witnessed by the proliferation of web sites devoted to it. Since many of the active ingredients in natural medicines are highly bioactive, the same concerns regarding environmental fate and ecological effects apply (Daughton and Ternes 1999) and should therefore be subjected to similar scrutiny. But the WHO strategy does not address any issues concerning disposal or pollution prevention.

In many countries, environmental risk assessments of varying degrees are required at least for new drug entities meeting certain criteria. While the existing regulations for these assessments (e.g., see discussions at: Velagaleti and Gill 2001; Velagaleti et al. 2002) as well as those under consideration (e.g., Health Canada 2002; CSTEE 2001) have the potential to evolve over time in response to new science regarding environmental impacts, similar assessments for dietary supplements, "alternative" medicines, and other personal care products do not exist. Given that the biological activity of many of these chemicals can rival that of drugs (e.g., see Daughton and Ternes 1999), it would be prudent to also submit these diverse chemical classes to environmental risk assessments; currently, they are completely free of any oversight regarding ecological hazard, no less human. Indeed, the fact that nutritional supplements can elicit profound biological effects is becoming codified in medical references (e.g., see: Thomson Medical Economics 2002a,b) where commonly recognized cross reactions with conventional drugs have already been noted — for example, with Saint John's wort (a potent inhibitor of certain drug-activating enzymes).

DRUG DELIVERY: Eco-friendly strategies to implement in the area of drug delivery include those relevant to prescribing, dispensing, patient compliance, and medication delivery mechanisms. A flavor for some advanced ideas regarding delivery mechanisms can be gained from Mort (2000).

Prescribing: Both physicians and the public could be made more aware and better informed as to the medical and environmental consequences of over-prescribing medications. Better ways need to be found to engage the medical community and the public in this issue. Guidelines could be developed and promulgated for minimizing inappropriate drug use (misuse, overuse, and abuse). With respect to the linkage between human and ecological health, progress on this front has been most well developed for the issue of antibiotics (see links at: Daughton/EPA 2002f), where physician knowledge and patient expectations are commonly at odds — antibiotics being prescribed (because of patient expectations) in

situations where antibiotics are not justified; imprudent use also extends to the practice of not identifying putative pathogens and performing susceptibility testing prior to selection of the most effective antibiotic. The literature continues to become more populated in documented circumstances where antibiotics have long been used but should not have been; a recent example is their inappropriate use for bronchitis (Evans et al. 2002). Minimization of the misuse of antibiotics also extends to veterinarians, aquaculturalists, and agriculturalists to lessen the incidence of resistance development in native bacteria and human pathogens (e.g., see Lipsitch et al. 2002; Smith et al. 2002). An example of a creative approach to minimizing the use of antibiotics for the common cold is presented by Arroll et al. (2002). By giving patients antibiotic prescriptions that could only be filled 3 days thence, overall usage was 48% as opposed to 89% for those having immediate access to antibiotics for "treating" common cold symptoms — nearly halving their usage and avoiding exposing the patient to unnecessary medication.

Lower vs. Established Dosing: There are numerous studies showing that the therapeutically effective dose for many drugs can be significantly lower than that initially recommended by the manufacturer. There are many reasons for this (including some stemming from regulatory requirements during clinical trials). They are summarized by Crutchfield (2001). Sometimes the effective dose for a drug can be many orders of magnitude lower than previously realized. This is largely a result of incomplete knowledge of MOAs. An excellent example is the conventional therapeutic dosage of morphine to achieve analgesia — typically about 1-10 mg/kg. With simultaneous administration of an opioid receptor antagonist (i.e., naltrexone) at the ultra-low dosage of 0.1 ng/kg, the same conventional level of analgesia can be achieved with morphine at 1 µg/kg — 6 orders of magnitude lower (a dosage that can be sustained without risk of addiction); similar effects can be achieved with 0.1 µg/kg of morphine coupled with 1 pg/kg naltrexone (Crain and Shen 2001; also see Pain Therapeutics 2002). This is an excellent example of research that could markedly reduce patient risk (by reducing side effects — adverse drug reactions [ADRs] — and even addiction), while minimizing the potential for environmental

effects. Most hospital ADR-related deaths are related to dose, and ADRs may be a leading cause of hospital death in the U.S. (Lazarou et al. 1998). Indeed, deaths from medication errors occurring both in and out of hospitals exceed 7,000 annually in the U.S. — exceeding those from workplace injuries (IOM 2000). Moreover, the IOM (2000) maintains that extrapolation of certain state-wide studies to the U.S. as a whole shows that annual excess costs of preventable hospital ADRs are about $2 billion (and hospital patients represent only a small portion of the at-risk general population).

Precision Formulation/Dosing: Current technology for formulating drug dosages is incapable of high accuracy or precision, especially that needed for ultra-low doses. Non-homogeneous formulation or inconsistent delivery can lead to undesirable repeated dosing and improper dosing (e.g., see: Alliance Pharmaceutical 2002). New technologies, such as "3D printing," are capable of formulating very accurate, precise, and minuscule amounts of drugs into one delivery device to achieve better temporal and spatial control of drug release via any combination of sustained, controlled, targeted, or cyclical methods. With the ability to control the drug release "profile" (tailored to a variety of factors including time after ingestion or circadian rhythm), more effective and lower doses can be achieved (see: MIT 3DPTM Laboratory 2002; MIT News 1997).

Individualization of Therapy: Drug manufacturers could provide the medical community with more easily implementable information (and requisite unit doses) to tailor drug dosages for the individual (especially for long-term maintenance drugs) on the basis of the sometimes complex interplay among body weight, age, sex, health status, nutritional status, timing/circadian rhythm, subtle genetic distinctions (e.g., accommodation for single-nucleotide receptor polymorphisms, SNPs — using new toxicogenomics tools), and known individual drug sensitivities; a number of companies are currently involved in approaches based on genetic variabilities to personalize drug therapy (e.g., Genaissance Pharmaceuticals 2002; Orchid Biosciences 2002; Variagenics 2002); currently, customized doses and formulations are

often obtainable only from private pharmacy "compounders" — not drug manufacturers — and are not subject to FDA rules for quality. Such individualization of therapy (also known as "calibrated dosing") can minimize the requisite therapeutic dose (which is frequently higher than need be) (Phillips et al. 2001). The human genome perhaps carries several million SNPs, an unknown portion of which can affect therapeutic outcomes. One nascent attempt to begin cataloging such SNPs is the Pharmacogenetics and Pharmacogenomics Knowledge Base (Altman 2002; Klein et al. 2001). Currently available tests for drug metabolizing enzymes (e.g., the cytochrome P450 [CYP] superfamily of monooxygenase isoforms) can distinguish fast, normal, and slow variants. These enzyme systems play major roles in the speed with which certain drugs are metabolized (whether leading to detoxication and excretion, or to activation) and therefore determine the proper dosage. Advances in detection of other physiologic and metabolic characteristics of a patient can also allow for the specific targeting of a drug for its intended site (to reduce unnecessary systemic exposure).

Individualized therapy can also help to address the growing trend of the healthy population that medicates on a long-term basis using a wide array of drugs as preventative measures (attempting to prevent the onset of various health problems). Outcomes from the use of medications by healthy people for durations spanning decades prompt numerous questions regarding safety (and the consequent issue of imprudent introduction of drugs to the environment). But long-term studies (those lasting for decades) are rarely ever performed because patents do not offer protection sufficiently long to justify the cost. It is possible that in place of new studies, the vast collection of individual, small reports already in the published literature could be distilled into useful knowledge. Much of what exists in the published literature is never "mined" and applied (Daughton 2001b, 2002b). An example of one step in the direction of mining the existing literature and using it to predict adverse drug outcomes is an approach called "evidence-based care," where recommendations are collectively made by physician experts who continually scan the broad

medical literature and synthesize recommendations (evidence-based rules) regarding drug usage across patients comprising a wide spectrum of health status (e.g., see: ActiveHealth Management 2002).

Develop Alternative Delivery Mechanisms: Dosages could be reduced with better targeted delivery routes (e.g., expanding the utility of pulmonary and trans-dermal/mucosal delivery), mechanisms of release (e.g., rapid-dissolving formulations, controlled release), and mechanisms for delivery of drugs to the target (e.g., antibody-linked drugs; in-situ implants) (e.g., see: Mort 2000); increasing attention is especially being devoted to nasal and pulmonary delivery (Burdick et al. 2000; Djupesland et al. 2002). Advancement in eluding the blood brain barrier would vastly expand the universe of available CNS drugs, which are currently restricted to a small galaxy of drugs smaller than 500 daltons; selective disruption of the blood-brain barrier, either via momentary enlargement of the endothelial cell junctions or by use of native membrane transporters is one example (Miller 2002). While advancement in drug delivery has received concerted attention over the years (e.g., see: ACS 2002; CRS 2002), expanded efforts in this area (for example, by leveraging with nanochemistry) could yield significant rewards, especially with respect to resurrection of "retired" or under-used drugs.

A potential future route/mechanism is the use of "click chemistry" for the self-assembly of drugs in-situ, where the non-bioactive precursor reactants required to synthesize a drug are self-assembled directly at the receptor target (the "templating" site; e.g., see: Borman 2002); such assembly that mimics enzyme-catalyzed synthesis is sometimes called "bioinspiration". This approach for drug delivery perhaps holds the ultimate potential for minimizing dosage. In-situ "click chemistry" (a new rendition of in-situ, site-catalyzed synthesis) uses the specific conformational locations within biochemical receptor molecules as "templates" for guiding the formation of a chemical product with high affinity for the site. Candidate drugs generated in this manner also would have a higher probability for specificity — avoiding the propensity for promiscuity ("dirty" drugs), a problem that has plagued drug discovery for years — and

thereby further reducing required doses (McGovern et al. 2002); interactions with receptors that do not provide intended therapeutic effects are sometimes called "sites of loss" and are often the cause of ADRs. The work done with current in-situ click chemistry shows the ease with which small molecules with ligand-interactions at the femtomolar level could be achieved. An acetylcholinesterase inhibitor formed via click chemistry proved to be the most potent noncovalent inhibitor ever found for this enzyme. Hypothetically, perhaps it will eventually prove possible to set the conditions for the self-assembly of reactants at the desired site of biochemical action within the living organism, to prevent reaction with non-target sites. Such an approach would effectively achieve the lowest possible dose for a drug (forming the ultimate "smart" drug), thereby minimizing or even eliminating the possibility for excretion to the environment.

Patient Compliance and Education: Patients frequently fail to finish their courses of medication — for a wide variety of reasons (see: "Take-Back Programs", Part II, Daughton 2003b). This problem not only increases health care costs and can jeopardize patient health, but it also leads to unnecessary accumulation of unused drugs, which then require disposal (this is a major problem at long-term care facilities; discussed in Part II, Daughton 2003b). Further education of patients might help in reducing patient non-compliance. Additional patient education regarding appropriate drug use (as defined by the United States Pharmacopeial Convention, USP [2001]) and drug abuse (consumption of more frequent or higher doses than prescribed, or use of illicit drugs) could help to reduce unnecessary excretion or disposal. A recent example of proactive guidance on minimizing commonly over-prescribed drugs is the CDC's campaign "Promoting Appropriate Antibiotic Use in the Community" (CDC 2002). By showing the linkages between human and ecological health benefits, perhaps more progress can be made in minimizing overuse/misuse of legal drugs (e.g., antibiotics) and illicit drugs; also of relevance is the linkages between illicit drug use and terrorism (see: Daughton/EPA 2001; ONDCP 2002).

Education of Health Care Practitioners: Hand-in-hand with education of the public is education of those working in the health care industry (not just pharmacists, but all health professionals and technicians, federal and state policy makers and regulators, organization managers and governing boards). A good way to teach the importance of dose minimization and proper disposal would be through formal, continuing education courses, where the interface between medicine and environmental science and the synergies accrued from cradle-to-cradle stewardship of medications could be taught. Along these lines, Smith (1999) proposed that the USP include hazardous waste criteria in its monographs; this recommendation could be extended to including disposal guidance for all non-hazardous, non-controlled drugs as well.

MARKETING:

Guidance on Packaging for Disposal: Consumer-oriented packaging for OTC and prescribed drugs in the U.S. lacks guidance for disposition of unused medication contents. Standardized nationwide guidance regarding recommended routes for responsible disposal (which could be custom-tailored depending on the ingredients) could be easily added to package labeling/inserts. The use of consumer guidance on labeling for protecting the environment has long been common with other consumer products throughout the world, especially for pesticides and industrial chemicals. Standards that cover the entire packaging system are developed and promulgated by the U.S. Pharmacopeial Convention, Inc. (USP). The many complex aspects of packaging are summarized by Okeke (2002). In the U.S., consumer warning and usage information regarding drugs is conveyed not just on affixed labels, but also on attendant documents such as prescription "leaflets," the minimum information content for which is set by the U.S. FDA. For prescription drugs, these leaflets are supposed to contain (at a minimum) the FDA-approved "Prescribing Information" (also called "Package Insert" or sometimes simply "PI"). Various other sources of consumer (as well as physician) information on drugs can be found in (1) the PDR ("Physicians' Desk Reference"), which contains the required prescribing information for most, but not all

drugs (the printed version is updated three times per year, the on-line version monthly, and the personal digital assistant version daily), (2) any of the various compendia such as "Drug Facts and Comparisons" (Facts and Comparisons 2002), which is updated with labeling changes monthly, and (3) MedWatch (U.S. FDA 2002b). The U.S. FDA's new labeling requirements for OTC drugs are one example of labeling status in the U.S. drugs (U.S. FDA 2002c). These are all examples of information resources that could convey information regarding possible environmental ramifications and disposal advice — comporting with the ideas of ecology of health and health of ecology.

Steps in this direction are already being taken. For example, EMEA (2001, section 5: "Precautionary and Safety Measures...") has already taken this step. A consumer survey sponsored by Health Canada showed that a large majority of respondents read drug labels but less than 50% read labels for personal care products (COMPAS 2002). Although the majority claim to read labels for ingredients, when unprompted by the interviewer, few (only 8%) claim to read them for information regarding "environmental-friendliness/impact". But when prompted, 57% said they do read labels for guidance regarding disposal (in Canada).

Guidance on Packaging to Prevent Unnecessary Dosing (aggregate & cumulative): Inadvertent ingestion of multiple drugs sharing the same MOA (joint action from cumulative exposure) or ingestion of the same drug from different sources (aggregate exposure) can occur when consumers use multiple medications without fully understanding the formulated contents. This multiple-exposure pathway scenario is especially problematic when patients are prescribed medications by multiple physicians; for patients with multiple healthcare providers, poor communication can also lead to re-prescribing of medication that has already been shown for the patient to by non-efficacious. In addition to prominently listing contents on labeling, it would also be useful to consumers to list the actual therapeutic endpoints. For example, analgesics are often formulated into multiple classes of medications, including those such as

painkillers, antihistamines, cold/flu preparations, and others, and consumers sometimes take all of these together, getting higher than needed doses. This could lessen the use of certain drugs and at the same time reduce the chances of consuming higher than necessary dosages. See Figure 2 for the differences between the various exposure scenarios (sometimes referred to as the Risk Cup). One possible mechanism for reducing this problem is presented in Part II (Daughton 2003b: "Personal 'Medical Statistics Card'").

More Informative & Less Confusing Drug Names: The Institute of Medicine (a private, nonprofit institution that provides health policy advice under a congressional charter granted to the National Academy of Sciences) recommends that better efforts be made to eliminate drug names that sound similar and formulated drugs that look similar, as well as confusing labels and packaging that foster mistakes by consumers, healthcare providers, and dispensers (IOM 2000). While these problems can jeopardize patient safety, they also lead to unnecessary (and inappropriate) use of drugs and their eventual discharge to the environment, as well as to the purchase of medications that might not have been made by a better-informed consumer.

Reducing Package Sizes: Consideration could be given to providing a broader selection of package sizes of PPCPs. Some PPCPs are perhaps more prone to being disposed because they are prescribed or purchased in quantities too great to be used before expiration or because they tend to expire more rapidly. A common example is aspirin and certain NSAIDs, which are available in such large package sizes that the contents may frequently go unused before reaching expiration. Alternatively, bulk-size packaging could incorporate individually factory-sealed sub-packages whose expiration dates are maintained even when the main-container seal is broken. Consumer education might also be useful here — to encourage purchase of only needed amounts of PPCPs (e.g., package sizes conducive to avoiding expiration). Consideration should therefore be given to not penalizing consumers monetarily for purchasing small-quantity package sizes (or perhaps offering "introductory size" samples).

Improved Packaging: Package materials and sealing mechanics could possibly be improved to enhance both factory-sealed and dispensed shelf-lives (e.g., more effective exclusion of humidity and heat, which are major factors limiting the storage life of drugs in bathrooms). Ideally, packaging could integrate inexpensive sensors (customized for each drug) that are capable of detecting breakdown products indicative of degraded drug performance or formation of products presenting adverse risk.

Advertising: Since the 1800s, PPCP direct-to-consumer (DTC) advertising in the U.S. has played an increasingly significant role in relaying information to the public regrading the many aspects of improved health, fitness, and appearance, as well as the prevention of disease (see history at: Duke University 2002). Only more recently have advertisers been required to highlight the caveats associated with their products (e.g., side effects or contraindications). DTC advertising purportedly empowers consumers, leading them to better-informed decisions and improved quality of care (e.g., see: National Health Council 2002; PhRMA 2001). But critics of DTC advertising (which is one of the most heated topics in the medical care industries of many countries) maintain that it can interfere with the physician-patient relationship (e.g., leading to "doctor shopping") and lead to the pressuring of physicians to prescribe expensive and sometimes unnecessary medications for demanding, poorly informed patients (Rosenthal et al. 2002); some countries have banned or minimized DTC advertising (e.g., see: Galbally 2000; Meek 2001). Regardless of the fate of DTC, a logical next step for advertisements could be to include information for the public regarding the proper disposition of unused products and what the imperative is for environmental stewardship.

Advertising can also help in educating consumers in decisions to use a new drug. A criticism of the reporting of controlled drug trials involves the significance of treatment outcomes. Two measures of significance are often used, not in conjunction with each other, but separately — without explaining their relative meanings. The measure of a new drug's effectiveness is usually expressed versus an accepted

standard treatment. If the new drug is more effective, its comparative effect can be expressed in terms of either Absolute Risk Reduction (ARR; or its reciprocal, Number Needed to Treat, NNT) or Relative Risk reduction (RRR). The citation of RRR often leads to seemingly much higher percentage effectiveness than citation of ARR (see discussion by Nuovo et al. 2002). Sometimes, while the RRR might convey to the consumer a major advance in treatment, in reality it might be minuscule in terms of absolute improvement (ARR) over current therapy.

DRUG DISPENSING:

Internet Dispensing: The availability of licit and also illicit drugs via the Internet (via both legal and illegal "Internet pharmacies") and black markets continues to escalate and expand, undoubtedly leading to over-dispensing and dispensing without a prescription (see: U.S. FDA 2002a). The added influx of drugs to the environment via illegal sales that were never anticipated by FDA during new drug approval is undoubtedly contributing to the overall environmental exposure burden; many of these sales come from overseas; this may have ramifications for performing environmental risk assessments for drugs (see below, "Geographic Variability in Drug Usage — Ramifications for Calculating EECs/PECs"). This also has profound ramifications for consumers in terms of safety and expense (e.g., "fake", counterfeit, or unstated dangerous ingredients), but it also would be a major factor in both the accumulation of unused drugs and the excretion of drugs that ordinarily might never have been ingested. Both the public and the pharmacy communities might benefit by more definitive education on these issues and to understand the possible environmental consequences. This could serve to minimize unneeded drug use and attendant disposal. One way for consumers to verify the quality of Internet pharmacies, is to check for the presence of the VIPPS hyperlink seal. The National Association of Boards of Pharmacy (NABP) association developed the certification program for Internet pharmacies called Verified Internet Pharmacy Practice Sites (VIPPS) program in 1999; few Internet pharmacies are VIPPS-certified (see NABP 2002).

Detection of Counterfeiting: Regarding the gray and black-market distribution of drugs, industry experts suggest that some 25% of the unauthorized distribution of pharmaceutical drugs takes place online (Cyveillance 2001). While development of deterrents for black-market distribution of drugs (and counterfeits) has always made economic sense for manufacturers (e.g., Green and Murray 2001), it would also clearly reduce the quantities of drugs available for eventual introduction to the environment (by both direct disposal and excretion). Advancements are needed in detecting molecular counterfeiting; an example is Biocode's anti-counterfeiting efforts (Biocode 2002).

Nationwide Database of Drug Sales: A publically accessible, central database that compiles and tracks geographic OTC and prescribed drug sales as well as drug usage (*not* to be misconstrued as a patient-level database) would be extremely useful for predicting the actual quantities of drugs that could be entering the environment (by making use of pharmacokinetic models based on ADME/Tox — adsorption, distribution, metabolism, excretion, and toxicity) (see: Daughton/EPA 2002g). Such a database would have great added utility for environmental scientists if it were integrated on a GIS platform to enhance the geographic utility of the data; first steps in this direction have been made and reported by Schowanek and Webb (2002). Data from the *Prescription Drug Atlas* (Express Scripts 2001) show that for some drugs, regional preferences in usage can vary by several fold. First steps in this direction include proprietary databases such as the extensive ones developed by Quintiles (2002a). The Quintiles "Market Monitor©" (Quintiles 2002b) uses near-real time patient claims transactions to mine accurate drug usage statistics at the geographic level.

Nationwide Database of Drug Returns: An active "returns" industry (see Part II, "Expanded Use and Mission of Reverse Distributors," Daughton 2003b) expanded to the consumer level would have obvious positive ramifications for the environment. Less appreciated, however, is that a cohesive nationwide policy encouraging the return of unused drugs to pharmacies or directly to reverse distributors

(see links at Daughton/EPA 2002h) has been shown to yield a number of consumer health and economic benefits by way of mining the data generated by a nationwide, integrated "returns" network. In the U.S., however, a morass of sometimes conflicting and competing oversight and liability concerns from numerous state and federal agencies stymies the creation of a cohesive approach to returning/recycling medication from the end user (see Part II, Daughton 2003b, "Responsible Re-Use, Recycling, Donation" for further discussion).

Geographic Variability in Drug Usage — Ramifications for Calculating EECs/PECs: As previously mentioned, environmental assessments for approval of NDAs (new drug applications) are required by the U.S. FDA only when the concentration of a drug predicted to enter the aquatic environment (environmental introduction concentration, EEC) would be 1 ppb or greater. But calculation of the EEC (or PEC) assumes a uniform usage of a drug across the U.S. Data from the *Prescription Drug Atlas* (Express Scripts 2001) show that for some drugs, regional preferences in usage can vary by several fold. This means that for highly populated metropolitan areas with usage of a particular drug exceeding what would be expected by a normal distribution, the EEC could be higher than predicted. This problem is further compounded by the fact that calculation of the EEC does not take into consideration cumulative exposure to drugs sharing the same mechanism of action — where the risk from a drug's non-target effects does not exist in insolation, but rather should at least be considered in the context of all drugs of like-mechanism of action. The calculation of EECs could be yielding underestimates also because of the expanding purchase and usage of drugs from the gray and black-markets, in large part via the Internet. These usage figures cannot currently be accounted for in environmental assessments.

Dispensing and Expiry: The disposal of drugs is necessitated by two major factors: (1) excess inventory of non-expired drugs (i.e., unwanted, unneeded but still usable drugs), and (2) out-dated drugs (those whose expiration [expiry] dates have been exceeded). Minimizing the need to dispose as a result of

these two factors can be addressed by minimizing inventory (by pharmacies and consumers alike) and by ensuring that expiration dates are based on actual, empirical data rather than projections. The issue of expiry is not as simple as it may seem, as there are a number of issues involved with setting the time periods for which a drug can be safely maintained (and these differ for factory-dispensed versus consumer unit-dispensed forms). In practice, the time periods for shelf-lives are determined not entirely empirically, but also by estimates and projections. Shelf-life is important as it dictates whether a therapeutic dose of the active ingredient is still present and whether degradation products with adverse therapeutic outcomes are absent.

(i) Conservative Dispensed Amounts: The need for disposal could be lessened by reducing prescribed/purchased quantities too great to be used before expiration, or increasing shelf life. Reasonable, minimal quantities of medication could be purchased or prescribed until the effects of the medication and its therapeutic effectiveness are understood by both the physician and patient. Over prescription of quantity (or frequent change in medication type) is a major reason for accumulation of unused drugs by geriatric patients (see Part II, "Take-Back Programs," Daughton 2003b). Consideration should be given to not penalizing consumers for small-quantity package sizes. This recommendation, however, runs counter to mail-order dispensing run by insurers, where multi-month supplies are favored because of short-term cost considerations.

(ii) Re-Engineering of Dispensing: A re-engineering of pharmacy practice with respect to the mechanics of drug dispensing could greatly reduce drug wastage. Progressing from previous advancements in dispensing (such as blister-packs, also known as "bingo-cards") and hospital unit-dose systems to the new generation of "automated medication dispensing" programs is demonstrated to have a dramatic impact not just on wastage, but also on reducing the hours required on the part of nurses and care givers devoted to mundane chores such as "med passing", and on assuring accurate medication distribution. This has been shown to be the case especially in long-term care facilities (LTCFs) where the accumulation of unused medications may be significant. An example is given by Saffel (1999). Certain

U.S. states such as Georgia do not allow return of unused portions of 30-day medication packages. A shorter 7-day exchange cycle provided by point-of-use "automated medication dispensing" obviates this problem (e.g., for an example of current technology, see Pyxis 2002). One of the recommendations of the IOM (2000) is that all hospitals and health care organizations implement the use of automated drug-ordering systems.

(iii) Science-Based Expiry Dates: Expiry dates could be investigated to see if they can be extended to reflect true stability durations. Scientifically sound protocols need to be implemented for the public sector to define, determine, predict, and/or monitor actual expiration periods for both factory-sealed and unsealed drugs. There have been very few scientific studies on the chemical stability of drugs in their formulated states. Guidance for establishing shelf-lives has been developed by the U.S. FDA (U.S. FDA 2001). The significant point, however, is that there is no requirement to establish the *maximum* shelf-life for a drug product — only to establish *a* documented shelf life. The major study, still on-going, for determining shelf-lives is the *Shelf-Life Extension Program* (U.S. DOD 2002), a stability testing program administered by the U.S. FDA for the U.S. Department of Defense (for non-civilian purposes). The SLEP has documented that the actual shelf lives for some drug formulations exceed the times dictated by the labeled expiration dates (under ideal storage conditions). The cost savings in being able to increase the life-cycle times for drug re-stocking purportedly claimed by the Department of Defense have been substantial.

The SLEP program has been highlighted by the AMA's Council on Scientific Affairs as the type of study requiring expansion (AMA 2001). The AMA emphasizes, however, that "Expiration dates only apply when the drug product is stored under defined conditions. Regardless of the feasibility of extending expiration dates, this strategy applies only to the date of packaging in the original factory container. For most U.S. drug products, expiration dating ranges from 12 to 60 months from the time of original manufacture." "Once the manufacturer's container is opened and drug product is transferred to another

container for dispensing or repackaging, the expiration date no longer applies. The USP has developed recommendations for pharmacists to place a 'beyond-use' date on the label of the new container. There is little scientific basis for 'beyond-use' dates. However, the American Pharmaceutical Association (APhA) encourages, and 17 states require, that pharmacists place a 'beyond-use' date on the label of the prescription container that is dispensed to the patient." See more detailed information presented by Okeke (2002).

Once the drug is transferred by a pharmacist to a consumer-use container (or heat-sealed blister pack), the pharmacist then applies an expiration date (usually one year from date of sale) not based on science; a USP standard for blister packs is 6 months or one-quarter of the manufacturer's original date (OSU 2000a, 2000b Exhibit 4). With this in mind, it would be beneficial when marketing larger-unit, bulk drugs (such as purchased by consumers in membership "club" warehouses) that the bulk container comprise a number of smaller, factory-sealed packages so as to extend the usable life. An article in *The Medical Letter* (1996) surmises that most medications stored in their original, unopened packaging under proper conditions retain 70-80% of their potency for at least 10 years. Once removed from original packaging, most tablets and capsules (dry-formulated drugs) retain 70-80% of their potency (in low humidity — i.e., preferably not in a humid bathroom, which is where most "medicine cabinets" reside) for 1-2 years after the expiration date. Note, however, that these points do not address the issue of consumer safety (e.g., changes in formulation quality), but rather point to the fact that chemical stability of the parent drug can be much longer than implied by expiration dates.

Reduce/Phase-Out Controversial Uses of Drugs: Historically, drugs or drug classes often undergo expanded usage beyond their original targeted purposes; this usually results from off-label prescribing. With certain other drugs or classes, the original intended use may have seemed logical at one time — only to be later challenged as unforeseen consequences emerged (as the known risk-benefit equation changed).

Respective examples of both scenarios are the post-menopausal use of combination hormone replacement therapy (HRT) and sub-therapeutic antibiotics in animal feed for growth promotion.

HRT's use in prevention of cardiovascular disease has long proved contentious. The long presumed benefits of combination HRT have been recently called into question by a number of studies, one of which is the 15-year "Women's Health Initiative" (WHI) sponsored by the National Institutes of Health (National Heart, Lung, and Blood Institute, NHLBI) [see various published papers and links provided at: NHLBI 2002]. The WHI study set out to examine the presumed long-term beneficial effects of combination HRT (involving estrogen and progestin) on the prevention of heart disease and hip fractures but instead the study was terminated prematurely when HRT was found instead to increase a woman's risk of breast cancer, heart attack, stroke, and blood clots; the study did find that HRT reduced the risk of colorectal cancer and bone fractures.

The long-running debates regarding the use of sub-therapeutic antibiotics and of anabolic steroids in animal feed have resulted in a number of actions in certain countries to set in place the wherewithal to reduce or abolish their usage. An example is the National Antimicrobial Resistance Monitoring System (NARMS), a joint nationwide monitoring program of the FDA, CDC, and USDA for detecting the extent and trends in both human and animal enteric bacteria susceptibilities to 17 antimicrobial drugs (CVM 2002; also see links at Daughton/EPA 2002f,i). From time to time, other drugs develop notoriety as a result of excessive or profound ADRs or other problems (thalidomide's original use is a classic example).

Vigilance and ongoing expedited review of the expansive literature (not limited solely to the various fields of medicine and health care, but also the biological and ecological literature) coupled with reasoned debate are important responsibilities of science for detecting possible future problems with respect to the use of new drugs and the continued use of established drugs, especially for those that provide non-

essential benefits. The soundness of current approaches used for determining whether drugs should be used for purposes never originally intended might benefit from continual re-evaluation.

CONCLUSIONS

The need for life-cycle stewardship of PPCPs is driven in part by the growing importance of preserving freshwater resources coupled with a water treatment and distribution infrastructure in need of major maintenance, repair, and upgrading. "Cradle-to-cradle" stewardship is prudent not just as a derivative of the Precautionary Principle and the concept of Environmental Surprise, but also because it holds the potential for major collateral benefits to consumer health care. In fact, parallels exist between human health care and the health of ecology. The options available for minimizing or preventing the release of PPCPs to the environment reside in a multitude of components composing the manufacturing and service sectors of the health care system — including everything from drug design, drug delivery, prescribing, dispensing, individualization of therapy, packaging, advertising, marketing, education for health care practitioners, and establishment of real-time PPCP usage databases, among many others. Regardless of the consequences of the current generation of PPCPs that continually make their way to the environment and add to the overall pollutant burden and play a role in exposed organisms' *Toxicant Totality Tolerance Trajectories*, we now have the knowledge and the opportunity to more thoroughly consider the potential for ecological or human health effects from new classes of drugs with unique mechanisms of biological action and to begin setting in place mechanisms for minimizing their introduction to the environment.

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Figure 1. "Limitations and Complexities of Environmental Chemical Analysis"

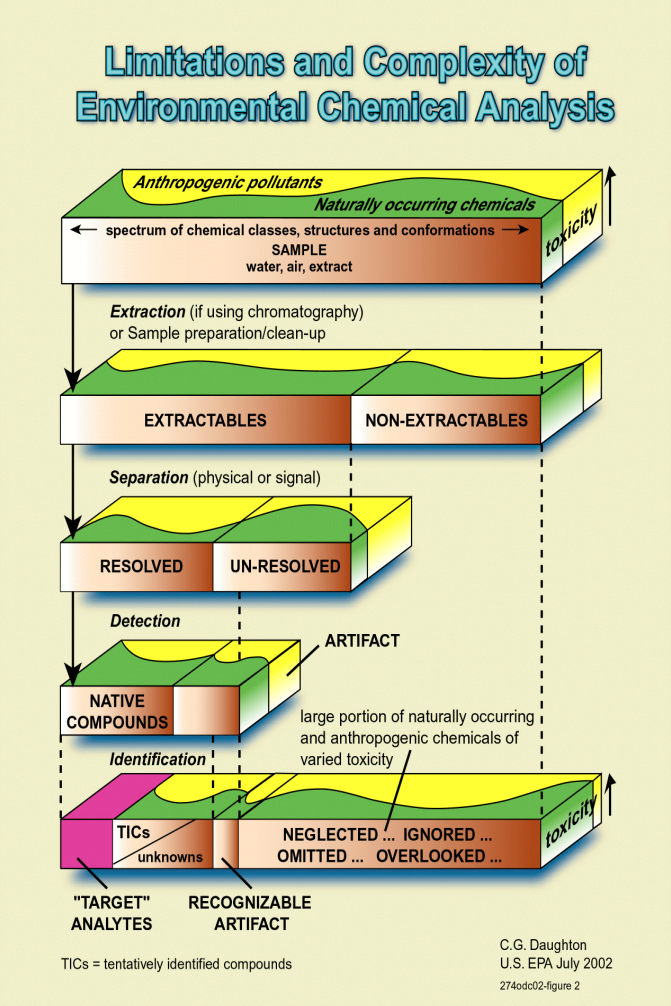

Figure 2. The "Risk Cup"